The innervation of the Heart
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The Innervation
Initiation of the cardiac cycle is myogenic, originating in the sinuatrial node (SA). It is harmonized in rate, force and output by autonomic nerves which operate on the nodal tissues and their prolongations, on coronary vessels and on the working atrial and ventricular musculature. All the cardiac branches of the N.vagus, X. cranial nerve, (parasympathetic) and all the sympathetic branches (except the cardiac branch of the superior cervical sympathetic ganglion) contain both afferent and efferent fibres; the cardiac branch of the superior cervical sympathetic ganglion is entirely efferent. Sympathetic fibres accelerate the heart and dilate the coronary arteries when stimulated, whereas parasympathetic (vagal) fibres slow the heart and cause constriction of coronary arteries.

Preganglionic cardiac SY (sympathetic) axons arise from neurones in the intermediolateral column of the upper four or five thoratic spinal segments. Some synapse in the corresponding upper thoratic SY ganglia, others ascend to synapse in the cervical ganglia; postganglionic fibres from these ganglia form the SY cardiac nerves (from ganglion cervicale sup. goes N.cardiacus cervicalis sup.; form ganglion cervicale med. Goes N.cardiacus cervicalis sup.; from ganglion cervicothoracicum(stellatum) goes N.cardiacus cervicalis inf.; from ganglion thoracicum I-IV go Nn.cardiaci thoracici).

Preganglonaric cardiac PSY (parasympathetic) axons arise from neurones in either the dorsal vagal nucleus ambiguous; they run in vagal cardiac branches to synapse in the cardiac plexuses and atrial walls. In man (like in most mammals) intrinsic cardiac neurones are limited to the atria and interatrial septum, and are most numerous in the subepicarial connective tissue near the SA and AV nodes.

There is evidence that these intrinsic ganglia are not simple nicotinic relays, but may act as sites for integration of extrinsic nervous inputs and form complex circuits for the local neuronal control of the heart, and perhaps even local reflexes.

Cardiac Plexus
Nearing the heart, the autonomic nerves form a mixed cardiac plexus, usually described in terms of a superficial component inferior to the arcus aortae lying between in and the truncus pulmonalis, and a deep part between the arcus aortae and tracheal bifurcation. The cardiac plexus is also described by regional names for its coronary, pulmonary, atrial and aortic extensions. These plexuses contain ganglion cells. Ganglion cells, confined to the atrial tissues, and with a preponderance adjacent to the SA node, are also found in the heart along the distribution of branches of the plexus. Their axons are considered to be largely, if not exclusively, postganglionic PSY. Cholinergic and adrenergic fibres, arising in or passing through the cardiac plexus, are distributed most profusely to the SA nad AV nodes; the supply to the atrial and ventricular myocardium is much less dense. Adrenergic fibres supply the coronary arteries and cardiac veins. Rich plexuses of nerves containing cholinesterase (an enzyme that hydrolyses acetylcholine into choline and acetic acid, found in heart, brain and blood), adrenergic transmitters and other peptides, e.g. neuropeptide Y, are found in the subendocardial regions of all chambers and in the cusps of the valves.

Superficial (ventral) part of the cardiac plexus
The superficial (ventral) part of the cardiac plexus lies below the arcus aortae and
anterior to the A.pulmonalis dex. It is formed by the cardiac branch of the left superior cervical SY ganglion and the lower of the two cervical cardiac branches of the N.vagus sin. A small cardiac ganglion is usually present in this plexus immediately below the arcus aortae, to the right of the lig.arteriosum. this part of the cardiac plexus connects with the deep part, the right coronary plexus and the left anterior pulmonary plexus.

**Deep (dorsal) part of the cardiac plexus**
The dorsal part of the cardiac plexus is anterior to the tracheal bifurcation, above the point of division of the truncus pulmonalis and posterior to the arcus aortae. It is formed by the cardiac branches of the cervical and upper thoracic SY ganglia and of the N.vagus and N.laryngeus recurrens. The only cardiac nerves that do not join it are those that join the superficial part of the plexus. Branches from the right half of the dorsal part of the cardiac plexus pass in front of and behind the A.pulmonalis dex. Those anterior to it, the more numerous, supply a few filaments to the right anterior pulmonary plexus and continue on to form part of the right coronary plexus. Those behind the A.pulmonalis supply a few filaments to the right atrium and then continue into the left coronary plexus. It forms much of the left coronary plexus.

**Left coronary plexus**
The left coronary plexus is larger that the right, and is formed chiefly by the prolongation of the left half of the dorsal part of the cardiac plexus and a few fibres from the right. It accompanies the left coronary artery to supply the atrium and ventriculus sin.

**Right coronary plexus**
The right coronary plexus is formed from both ventral and dorsal parts of the cardiac plexus, and accompanies the right coronary artery to supply the atrium and ventriculus dex.
and, at the same time, increased activity. Adrenergic stimulation (stimulated by adrenaline) of the SA node and conducting tissue increases the rate of depolarization of the pacemaker cells while increasing AV conduction. SY ganglionic fibers release neurotransmitter the catecholamine norepinephrine, which binds to α or β receptors on the presynaptic noradrenergic nerve terminal, or on the postsynaptic membrane of the target organ. An exception to this general rule is the presence in the sympathetic division of postganglionic fibers, which innervate the sweat glands. These are cholinergic, and release ACh, which acts on muscarinic receptors on the membranes of the sweat glands. Direct adrenergic stimulation from the SY nerve fibres, as well as indirect suprarenal (adrenal) hormone stimulation, increases atrial and ventricular contractility. Most adrenergic receptors on coronary blood vessels are β₂-receptors, which, when activated, cause relaxation (or perhaps inhibition) of vascular smooth muscle and, therefore, dilatation of the arteries. This supplies more oxygen and nutrients to the myocardium during periods of increased activity.

PSY fibers are found associated with blood vessels in certain organs such as salivary glands, gastrointestinal glands, and in genital erectile tissue. The release of acetylcholine (ACh), which binds to nicotinic receptors on ganglionic postsynaptic cell bodies of postganglionic fibers, from these PSY nerves has a direct vasodilatory action (coupled to nitric oxide formation and guanylyl cyclase activation). ACh release can stimulate the release of kallikrein (serine protease) from glandular tissue that acts upon kininogen to form kinins, e.g. bradykinin (any of a group of vasoactive straight-chain polypeptides formed by kallikrein-catalyzed cleavage of kininogens). Kinins cause increased capillary permeability and venous constriction, along with arterial vasodilation in specific organs. The PSY supply is from presynaptic fibres of the N.vagus. Postsynaptic PSY cell bodies (intrinsic ganglia) are located in the atrial wall and interatrial septum near the SA and AV nodes and along the coronary arteries, savig energy between periods of increased demand. Postsynaptic PSY fibres release ACh, which binds with muscarinic receptors to slow the rates of depolarisation of the pacemaker cells and atrioventricular conduction and decrease atrial contractility.

Neural Activation of the Heart and Blood Vessels

Activation of SY efferent nerves to the heart increases heart rate (positive chronotropy), contractility (positive inotropy), rate of relaxation (increased lusitropy), and conduction velocity (positive dromotropy). PSY effects are opposite. PSY effects on inotropy are weak in the ventricle, but relatively strong in the atria. Physiologically, whenever the body activates the sympathetic system, it down regulates PSY activity, and visa versa, so that the activities of these two branches of the autonomic nervous system respond reciprocally.

In blood vessels, SY activation constricts arteries and arterioles (resistance vessels), which increases resistance and decreases distal blood flow. SY-induced constriction of veins (capacitance vessels) decreases venous compliance and blood volume, and thereby increases venous pressure. Most blood vessels in the body do not have PSY innervation. However, PSY nerves do innervate salivary glands, gastrointestinal glands, and genital erectile tissue where they cause vasodilation. The overall effect of SY activation is to increase cardiac output, systemic vascular resistance (both arteries and veins), and arterial blood pressure. Enhanced SY activity is particularly important during exercise, emotional stress, and during hemorrhagic shock.

The actions of autonomic nerves are mediated by the release of neurotransmitters that bind to specific cardiac receptors and vascular receptors. These receptors are coupled to signal transduction pathways that evoke changes in cellular function.
Adrenergic and Cholinergic Receptors in Cardiac Muscle

SY adrenergic nerves innervate the SA and AV nodes, conduction pathways, and myocytes in the heart. These adrenergic nerves release the neurotransmitter norepinephrine (NE), which binds to specific receptors in the target tissue to produce their physiological responses. Neurotransmitter binding to receptors activates signal transduction pathways that cause the observed changes in cardiac function.

Adrenergic receptors (adrenoceptors) are receptors that bind adrenergic agonists such as the SY neurotransmitter NE and the circulating hormone epinephrine (EPI). The most important adrenoceptor in the heart (not including coronary vascular adrenoceptors) is the β₁-adrenoceptor. When activated by a β₁-agonist such as NE or EPI, heart rate is increased (positive chronotropy), conduction velocity is increased (positive dromotropy), contractility is increased (positive inotropy), and the rate of myocyte relaxation is increased (positive lusitropy).

There are also β₂-adrenoceptors in the heart and stimulation by β₂-agonists has similar cardiac effects as β₁-adrenoceptor stimulation. The β₂-adrenoceptors become functionally more important in heart failure because β₁-adrenoceptors become down regulated.

NE can also bind to α₁-adrenoceptors found on myocytes to produce small increases in inotropy. Circulating catecholamines (epinephrine) released by the adrenal medulla also binds to these same alpha and beta adrenoceptors on the heart on myocytes. In addition to SY adrenergic nerves, the heart is innervated by PSY cholinergic nerves derived from the N.vagus. ACh released by these fibers binds to muscarinic receptors in the cardiac muscle, especially at the SA and AV nodes that have a large amount of vagal innervation. ACh released by N.vagus binds to M₂ muscarinic receptors, a subclass of cholinergic receptors. This produces negative chronotropy and dromotropy in the heart, as well as negative inotropy and lusitropy in the atria (the negative inotropic and lusitropic effects of vagal stimulation are relatively weak in the ventricles).

The autonomic nerve terminals also possess adrenergic and cholinergic receptors (prejunctional receptors) that function to regulate the release of NE (not shown in figure). Prejunctional α₂-adrenoceptors inhibit NE release, whereas prejunctional β₂-adrenoceptors facilitate NE release. Prejunctional M₂ receptors inhibit NE release, which is one mechanism by which vagal stimulation overrides SY stimulation in the heart.

Drugs are available for blocking adrenergic and cholinergic receptors. For example, beta-blockers are used in the treatment of angina, hypertension, arrhythmias, and heart failure. Muscarinic receptor blockers such as atropine are used to treat electrical disturbances (e.g. bradycardia and conduction blocks) associated with excessive vagal stimulation of the heart. Many of these adrenergic and cholinergic blockers are relatively selective for a specific receptor subtype.

Atropine (Muscarinic Receptor Antagonist)

N.vagus nerves that innervate the heart release ACh as their primary neurotransmitter. ACh binds to muscarinic receptors (M₂) that are found principally on cells comprising the (SA) and (AV) nodes. Muscarinic receptors are coupled to the Gi-protein; therefore, vagal activation decreases cAMP. Gi-protein activation also leads to the activation of KₐCh channels that increase potassium efflux and hyperpolarizes the cells. Increases in vagal activity to the SA node decreases the firing rate of the pacemaker cells by decreasing the slope of the pacemaker potential (phase 4 of the action potential); this decreases heart rate (negative chronotropy). The change in phase 4 slope results from alterations in potassium and calcium currents, as well as the slow-inward sodium current.
that is thought to be responsible for the pacemaker current (\(I_h\)). By hyperpolarizing the cells, vagal activation increases the cell’s threshold for firing, which contributes to the reduction the firing rate. Similar electrophysiological effects also occur at the AV node; however, in this tissue, these changes are manifested as a reduction in impulse conduction velocity through the AV node (negative dromotropy). In the resting state, there is a large degree of vagal tone on the heart, which is responsible for low resting heart rates. There is also some vagal innervation of the atrial muscle, and to a much lesser extent, the ventricular muscle. N. vagus activation, therefore, results in modest reductions in atrial contractility (inotropy) and even smaller decreases in ventricular contractility.

Muscarinic receptor antagonists bind to muscarinic receptors thereby preventing ACh from binding to and activating the receptor. By blocking the actions of ACh, muscarinic receptor antagonists very effectively block the effects of vagal nerve activity on the heart. By doing so, they increase heart rate and conduction velocity.

**Beta-Adrenoceptor Antagonists (Beta-Blockers)**

Beta-blockers are drugs that bind to beta-adrenoceptors and thereby block the binding of NE and EPI to these receptors. This inhibits normal sympathetic effects that act through these receptors. Therefore, beta-blockers are sympatholytic drugs. Some beta-blockers, when they bind to the \(\beta\)-adrenoceptor, partially activate the receptor while preventing NE from binding to the receptor. These partial agonists therefore provide some “background” of SY activity while preventing normal and enhanced SY activity. These particular beta-blockers (partial agonists) are said to possess intrinsic sympathomimetic activity (ISA). Some beta-blockers also possess what is referred to as membrane stabilizing activity (MSA). This effect is similar to the membrane stabilizing activity of sodium-channels blockers that represent Class I antiarrhythmics.

The first generation of beta-blockers were non-selective, meaning that they blocked both \(\beta_1\) and \(\beta_2\) adrenoceptors. Second generation beta-blockers are more cardioselective in that they are relatively selective for \(\beta_1\) adrenoceptors. Note that this relative selectivity can be lost at higher drug doses. Finally, the third generation beta-blockers are drugs that also possess vasodilator actions through blockade of vascular \(\alpha\)-adrenoceptors.

**Heart:** Beta-blockers bind to \(\beta\)-adrenoceptors located in cardiac nodal tissue, the conducting system, and contracting myocytes. The heart has both \(\beta_1\) and \(\beta_2\) adrenoceptors, although the predominant receptor type in number and function is \(\beta_1\). These receptors primarily bind NE that is released from SY adrenergic nerves. Additionally, they bind NE and EPI that circulate in the blood. Beta-blockers prevent the normal ligand (NE or EPI) from binding to the \(\beta\)-adrenoceptor by competing for the binding site.

\(\beta\)-adrenoceptors are coupled to a Gs-proteins, which activate adenylyl cyclase to form cAMP from ATP. Increased cAMP activates a cAMP-dependent protein kinase (PKA) that phosphorylates L-type calcium channels, which causes increased calcium entry into the cell. Increased calcium entry during action potentials leads to enhanced release of calcium by the sarcoplasmic reticulum in the heart; these actions increase inotropy. Gs-protein activation also increases heart rate (chronotropy). PKA also phosphorylates sites on the sarcoplasmic reticulum, which lead to enhanced release of calcium through the ryanodine receptors (ryanodine-sensitive, calcium-release channels) associated with the sarcoplasmic reticulum. This provides more calcium for binding the troponin-C, which enhances inotropy. Finally, PKA can phosphorylate myosin light chains, which may contribute to the positive inotropic effect of \(\beta\)-adrenoceptor stimulation.

Because there is generally some level of SY tone on the heart, beta-blockers are able to reduce SY influences that normally stimulate chronotropy, inotropy, dromotropy and lusitropy. Therefore, beta-blockers cause decreases in heart rate, contractility, conduction velocity, and relaxation rate.
These drugs have an even greater effect when there is elevated SY activity.

**Signal Transduction Mechanisms**

The regulation of cardiac and vascular function depends on various substances (e.g. neurotransmitters, circulating hormones, paracrine substances) signaling a cell to alter its function. Generally, this is accomplished through the binding of a chemical entity (ligand) to a receptor, most commonly located on the cell membrane. When a ligand binds to a receptor, the receptor signals biochemical changes within the cell that can lead to changes, for example, in muscle contraction, the firing of cardiac pacemakers, or the conduction of electrical impulses in the the heart.

There are several major signal transduction mechanisms found in cells of the cardiovascular system, the most important being the G-protein, IP₃, and cyclic GMP pathways.

**Gs-Protein and Gi-Protein Coupled Signal Transduction:**

G-proteins are linked to an enzyme, adenylyl cyclase, that dephosphorylates ATP to form cyclic AMP (cAMP). Gs-protein (stimulatory G-protein) activation (e.g. via β-adrenoceptors) increases cAMP. This activates PKA (cAMP stimulated protein kinase) and causes increased influx of Ca²⁺ by phosphorylation and activation of L-type calcium channels, and enhanced release of Ca²⁺ by the sarcoplasmic reticulum in the heart. These and other intracellular events increase inotropy, chronotropy, dromotropy and lusitropy. Activation of Gi-proteins (inhibitory G-protein), for example by adenosine and muscarinic receptor activation, decreases cAMP and PKA activation, decreases Ca²⁺ entry and release, and increases outward, hyperpolarizing K⁺ currents. Activation of the Gi-protein pathway therefore enhances repolarization.

Gi-protein activation produces effects that are opposite to those elicited by Gs-protein activation; however, Gi-protein effects are primarily directed toward the SA node and AV node to decrease sinus rate and AV nodal conduction velocity, respectively, with minimal effects on muscle contractility. In contrast, Gs-protein strongly stimulates muscle contraction in addition to its nodal effects.

**IP₃-Coupled Signal Transduction:**

The IP₃ pathway is linked to activation of α₁-adrenoceptors, angiotensin II (AII) receptors, and endothelin-1 (ET-1) receptors and therefore is stimulated by α-agonists, angiotensin II and endothelin-1. These receptors are coupled to a phospholipase C (PLC)-coupled Gq-protein, which when activated, stimulates the formation of inositol trisphosphate (IP₃) from phosphatidylinositol biphosphate (PIP₂). Increased IP₃ stimulates Ca²⁺ release by the sarcoplasmic reticulum in the heart, thereby increasing inotropy as one of its actions.
Altered Signal Transduction in Heart Disease:

Altered signal transduction mechanisms have a significant role in the loss of inotropy in heart failure. For example, desensitization of $\beta_1$-adrenoceptors in the heart decreases inotropic responses to SY activation. Uncoupling of the $\beta_1$-adrenoceptor and the Gs-protein reduces the ability to activate adenylyl cyclase. If the ability of PKA to phosphorylate L-type calcium channels is impaired, then calcium influx into the cell would be reduced, leading to a smaller release of calcium by the sarcoplasmic reticulum. Reduced calcium release would impair excitation-contraction coupling, thereby decreasing inotropy.

Impulse Conduction

The action potentials generated by the SA node spread throughout the atria primarily by cell-to-cell conduction at a velocity of about 0.5 m/sec. There is some functional evidence for the existence of specialized conducting pathways within the atria (termed internodal tracts), although this is controversial. As the wave of action potentials depolarizes the atrial muscle, the cardiomyocytes contract by a process termed excitation-contraction coupling.

Normally, the only pathway available for action potentials to enter the ventricles is through a specialized region of cells (AV node) located in the inferior-posterior region of the interatrial septum. The AV node is a highly specialized conducting tissue (cardiac, not neural in origin) that slows the impulse conduction considerably (to about 0.05 m/sec) thereby allowing sufficient time for complete atrial depolarization and contraction (systole) prior to ventricular depolarization and contraction.

The impulses then enter the base of the ventricle at the Bundle of His and then follow the left and right bundle branches along the interventricular septum. These specialized fibers conduct the impulses at a very rapid velocity (about 2 m/sec). The bundle branches then divide into an extensive system of Purkinje fibers that conduct the impulses at high velocity (about 4 m/sec) throughout the ventricles. This results in rapid depolarization of ventricular myocytes throughout both ventricles.

The conduction system within the heart is very important because it permits a rapid and organized depolarization of ventricular myocytes that is necessary for the efficient generation of pressure during systole. Atrial activation is complete within about 0.09 sec (90 msec) following SA nodal firing. After a delay at the AV node, the septum becomes activated (0.16 sec). All the ventricular mass is activated by about 0.23 sec.

Regulation of conduction

The conduction of electrical impulses throughout the heart, and particularly in the specialized conduction system, is influenced by autonomic nerve activity. This autonomic control is most apparent at the AV node. SY activation increases conduction velocity in the AV node by increasing the rate of depolarization (increasing slope of phase 0) of the action potentials. This leads to more rapid depolarization of adjacent cells, which leads to a more rapid conduction of action potentials (positive dromotropy). SY activation of the AV node reduces the normal delay of conduction through the AV node, thereby reducing the time between atrial and ventricular contraction. The increase in AV nodal conduction velocity can be seen as a decrease in the P-R interval of the electrocardiogram.

SY nerves exert their actions on the AV node by releasing the neurotransmitter norepinephrine that binds to $\beta$-adrenoceptors, leading to an increase in intracellular cAMP. Therefore, drugs that block beta-
adrenoceptors (beta-blockers) decrease conduction velocity and can produce AV block. PSY (vagal) activation decreases conduction velocity (negative dromotropy) at the AV node by decreasing the slope of phase 0 of the nodal action potentials. This leads to slower depolarization of adjacent cells, and reduced velocity of conduction. ACh, released by the N.vagus, binds to cardiac muscarinic receptors, which decreases intracellular cAMP. Excessive vagal activation can produce AV block. Drugs such as digitalis, which increase vagal activity to the heart, are sometimes used to reduce AV nodal conduction in patients that have atrial flutter or fibrillation. These atrial arrhythmias lead to excessive ventricular rate (tachycardia) that can be suppressed by partially blocking impulses being conducted through the AV node.

Phase 0 of action potentials at the AV node is not dependent on fast sodium channels as in non-nodal tissue, but instead is generated by the entry of calcium into the cell through slow-inward, L-type calcium channels. Blocking these channels with a calcium-channel blocker such as verapamil or diltiazem reduces the conduction velocity of impulses through the AV node and can produce AV block. Because conduction velocity depends on the rate of tissue depolarization, which is related to the slope of phase 0 of the action potential, conditions (or drugs) that alter phase 0 will affect conduction velocity. For example, conduction can be altered by changes in membrane potential, which can occur during myocardial ischemia and hypoxia. In non-nodal cardiac tissue, cellular hypoxia leads to membrane depolarization, inhibition of fast Na+ channels, a decrease in the slope of phase 0, and a decrease in action potential amplitude. These membrane changes result in a decrease in speed by which action potentials are conducted within the heart. This can have a number of consequences. First, activation of the heart will be delayed, and in some cases, the sequence of activation will be altered. This can seriously impair ventricular pressure development. Second, damage to the conducting system can precipitate tachyarrhythmias by reentry mechanisms.

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